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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 40-44, and 46-49 are rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 40-44, and 46-49 are vague and indefinite in their recitation of "wherein one or more cysteine residues is deleted or replaced by alanine or serine and wherein said cysteine residues are selected from the group consisting of amino acid positions 1, 13, 72, 101, 126, 128, 133, 138, 146, 167 and 175 in Figure 2", and "wherein one or more tyrosine residues is replaced by phenylalanine and wherein said tyrosine residues are selected from the group consisting of amino acid positions 36, 45, 64, 84, 122, 139 and 178 in Figure 2". Which cysteine residues are replaced? Which cysteine residues are deleted? Which tyrosine residues are replaced? Attention is directed to Ex parte Tanksley (26 USPQ2d 1384) wherein the Board noted that, under 35 USC 112, second paragraph, the claims must be so definite as to allow their comparison with the available art and must also make it possible for the public to determine from the claims what it is they comprehend. It is asserted that a member of the public would not know what chemical structure is intended by that which is claimed.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

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connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

Specific basis is lacking in the specification for the recitation of "wherein one or more cysteine residues is deleted or replaced by alanine or serine and wherein said cysteine residues are selected from the group consisting of amino acid positions 1, 13, 72, 101, 126, 128, 133, 138, 146, 167 and 175 in Figure 2", and "wherein one or more tyrosine residues is replaced by phenylalanine and wherein said tyrosine residues are selected from the group consisting of amino acid positions 36, 45, 64, 84, 122, 139 and 178 in Figure 2". Thus, the recitation is considered to be new matter. Moreover, applicants point to Figure 2 for support of their newly amended claims, however, the Figure merely sets forth the sequence of the native inhibitor. That is, the examiner cannot find support for the deleted or replaced cysteine residues at the recited positions. Please see MPEP 608.04 and 706.03(o).

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

The scope of the claims is broader than the enablement provided by the specification. That is, variants of the instant enzyme inhibitor are claimed, however, the specification fails in teaching specific substituted or deleted polypeptides (or DNAs which encode said polypeptides) having the claimed characteristics. No guidance is provided as to which cysteine residues of the disclosed polypeptide can be modified without changing the activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of polypeptides broadly encompassed by the claims. Predictability of which changes can

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be tolerated in a protein's amino acid sequence while retaining similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (see the whole publication of Bowie et al. 1990. Science, Vol 247, pp. 1306-1310, particularly p. 1306 and column 2 of p. 1308).

While recombinant and mutagenesis techniques are known and it is known that some proteins can tolerate a number of amino acid substitutions (i.e. predominantly in non-conserved amino acids), the positions within the protein's sequence where such amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited and such modifications are unpredictable in the absence of further guidance. Other positions in the sequence of such proteins are critical to the protein's structure/function relationship, e.g. such as various positions or regions directly involved in binding, catalysis or other activity and in providing the correct three-dimensional spacial orientation of binding and/or catalytic sites, and one skilled in the art would expect any tolerance of a given protein to modification to decrease with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed DNAs encoding the polypeptide(s), for the reasons discussed

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the claims would still expectedly encompass a significant number of inoperative species which could not be distinguished without undue experimentation.

While enablement can be supported even if some experimentation is required, such experimentation must be merely routine and if the results to be obtained are unpredictable the experimentation is not routine, but rather undue. Applicants have not taught where the critical cysteine residues are in the instant polypeptide or related polypeptides having the same activity nor what amino acids are conserved in the particular claimed polypeptides nor the structural requirements for producing compounds of similar activity. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). Recently, in Ex parte Maize! (27 USPQ2d 1662), the Board considered that claims encompassing such biologically functional equivalents were analogous to a single means claim and as such were more broad than the disclosure which disclosed only a single specific DNA segment known to the inventor. Such is the case here in which the specification is considered enabling only for claims limited to the specific nucleic acid sequence given in Figure 2.

Claims 40-44, and 46-49 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Applicant's arguments with respect to claims 40-44, and 46-49 have been considered but are moot in view of the new ground(s) of rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for response to this final action is set to expire **THREE MONTHS** from the date of this action. In the event a first response is filed within **TWO MONTHS**

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of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laurie Scheiner whose telephone number is (703) 308-1122.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM 1 Fax Center number is (703) 305-7939.


Laurie Scheiner/LAS
February 17, 1997


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